

### REMARKS

Applicants have amended the Abstract to recite that the process comprises condensing an aldehyde 17 with 6-bromo-penem derivative of structure 16.

Applicants have amended claims 1, 4-6, 8, 13-30, 32, 34, and 41 and have canceled claim 7.

None of these amendments adds any new matter. Their entry is respectfully requested.

### Election/Restriction

The Examiner has required restriction of the claims under 35 U.S.C. § 121 into the following two groups:

Group I. Claims 1-30, 32-42, drawn to processes; and

Group II. Claim 31, drawn to product.

Applicants affirm the provisional election of Group I, claims 1-30 and 32-42, drawn to processes.

### Rejection Under 35 U.S.C. § 112

Claims 1-30 and 32-42 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contends that:

1. The term "mild base" is indefinite.
2. The term "low temperature" in claim 1 is indefinite.
3. The term "mild temperature" in claim 7 is indefinite.
4. The second choice in claim 6 is "not possible" because there is no choice of R<sub>8</sub> as haloalkylsulfonyl.
5. Formula 7-A of claim 18, formula 8-A of claim 9, formula 9-A of claim 10, formula 15-A of claim 16, etc. are poorly drawn.
6. Step (a) in claim 32 "makes no sense as written" because the brominating agent was left out.
7. The phrase "appropriately substituted" in the definition of A' is unclear.

8. The  $R_6$ - $R_7$  combined option "is not correct" because it should say "[t]ogether with the N to which they are attached form a ..." and the heteroatoms are not optional.

9. – 37. Certain provisions for the Y and Z groups of claims 14—30 are not possible in order to retain the aromatic character of the ring.

Applicants respectfully traverse each of the rejections. Solely to expedite prosecution and without acquiescing to the propriety of the rejection, Applicants have amended the claims as outlined below. Applicants' enumerated comments below parallel the enumerated rejections made by the Examiner.

1. Applicants have amended the claims at each instance to delete the term "mild base," and to recite "organic tertiary base." Support for this amendment appears throughout the specification as filed, *e.g.*, p. 7, lines 22-23.

2. Applicants have amended the claims at each instance to delete the term "low temperature," and to recite "a temperature of -10°C to -40°C." Support for this amendment appears throughout the specification as filed, *e.g.*, p. 7, line 24.

3. Applicants have canceled claim 7, and have amended claim 8 to incorporate the language of former claim 7 and to delete the term "mild temperature."

4. Applicants have amended claim 6 to delete the term "triflate."

5. Applicants respectfully submit that the structural formulae of all the claims are acceptable and definite.

6. Applicants have amended step (a) in claim 32 to recite that dissolving the 6-APA water and organic solvent takes place in the presence of hydrobromic acid and sodium or potassium nitrite solution. Support for this amendment appears throughout the specification as filed, *e.g.*, p. 5, lines 13-16, Scheme A, p. 35, lines 24-26, Scheme 3, p. 40, lines 10-13; and in claim 34.

7. Applicants have amended claims 1 and 41 to delete the term "appropriately substituted."

8. Applicants have amended  $R_6$  and  $R_7$  at each instance to recite that " $R_6$  and  $R_7$  together with the N to which they are attached, may form a 3-7 membered saturated ring system said ring system in addition to the N to which  $R_6$  and  $R_7$  are attached optionally having one or two heteroatoms." Applicants make these amendments solely to expedite prosecution, and

believe that one of skill in the art would have understood the original language to have the same scope and meaning as the amended language.

9. – 37. Applicants have amended claims 14-30 in response to the Examiner's comments with respect to the various Y and Z substituents. Applicants make these amendments solely to expedite prosecution, and believe that one of skill in the art would have understood the original language to have the same scope and meaning as the amended language.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

### **Rejection Under 35 U.S.C. § 103**

Claims 1-8, 12, 32-33 and 36-42 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over EP 232966, either alone or in view of McOmie, *Protective Groups in Organic Chemistry*, p. 198 ("McOmie") or U.S. Patent No. 4,891,369 ("the '369 patent"), and also in view of U.S. Patent No. 6,268,393 ("the '393 patent"). Specifically, the Examiner contends as follows:

A. The Examiner states that the starting material of the prior art differs from the starting material of the claims in that it has a slightly different protecting group (p-methoxybenzyl versus p-nitrobenzyl). (Office Action, p. 8, last para.) The Examiner further states that EP 232966 teaches that both of these protecting groups are suitable and therefore any of the listed protecting groups would be obvious variants of the p-methoxybenzyl species that appears in the reference. (Office Action, p. 8, last para.) The Examiner states that McOmie or the '369 patent teach the advantages of the p-nitrobenzyl. In particular, the Examiner states that McOmie teaches that the p-nitrobenzyl group is more stable to acids than the p-methoxybenzyl group, and that U.S. Patent No. 4,891,369 exemplifies a penicillin carboxyl-protecting group of p-nitrobenzyl. (Office Action, p. 9, 1<sup>st</sup> para.) The Examiner, therefore, concludes that Applicants must show unexpected effects arising from the use of one p-substituted benzyl rather than another to overcome this rejection. (Office Action, p. 9, 1<sup>st</sup> para.)

B. The Examiner also states that Applicants' claimed aldol condensation is "a slightly different procedure" from the references in that EP 232966 uses lithium amide bases,

while the present claims use a mild base and a Lewis acid.<sup>1</sup> (Office Action, p. 9, 2<sup>nd</sup> para.) The Examiner states that the '393 patent "teaches exactly such an equivalence in an aldol reaction." (Office Action, p. 9, 2<sup>nd</sup> para.) The Examiner also indicates that the '393 patent states that instead of LDA, "other bases such as amines can be used; and MgBr<sub>2</sub> [*sic*] appears as an auxiliary .... This is the exact variation that applicants employ. Thus, such a variation is obvious."

The Examiner states that for claims 32-33 and 36-40, point A. is not a difference, because these claims do permit the p-methoxybenzyl group.

The Examiner states that claims 32-33 and 36-40 additionally provide for the synthesis of the penem 16. The Examiner also states that the first part of step (a) of claim 16 "has been ignored, as it makes no sense." The Examiner states however that claim 34 has not been rejected, and that inserting the text of the second line of claim 34 into the first part of step (a) of claim 32 would overcome the rejection.

Applicants respectfully traverse the rejections. Applicants' comments below address the Examiner's points A. and B. in turn.

A. Applicants respectfully submit that the specification as filed shows the unexpected effects arising from the use of the p-nitrobenzyl protecting group of the claimed starting material, as required by the Examiner.

In particular, the specification as filed notes that the p-nitrobenzyl protected compound is a crystalline derivative, and the crystalline nature of the compound imparts stability and increases shelf-life time (p. 7, lines 13-14). Moreover, the specification provides specific comparative thermal stability data for the p-nitrobenzyl protected compound as compared to the same compound having a p-methoxybenzyl protecting group (p. 31, lines 1-15 and Table 1). As noted in Table 1, the increased stability of the p-nitrobenzyl protected compound as compared to the p-methoxybenzyl protected compound enhances the shelf-life of the claimed compound (p. 31, lines 8-10 and Table 1). Further still, the specification as filed notes that the p-nitrobenzyl protecting group of the claimed starting material permits the subsequent reductive elimination

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<sup>1</sup> While the Office Action at p. 9, 2<sup>nd</sup> para. recites that "[t]he current claims use a 'mild base,' ... plus a Lewis base, e.g. Mg salt" Applicants respectfully submit that the claims recite a Lewis acid, rather than a Lewis base.

and deprotection to take place in a single step, rather than a two-step procedure as can be followed for compounds having other protecting groups (p. 28, line 31 to p. 29, line 2).

Thus, Applicants' starting material and pending claims related thereto are non-obvious in view of EP 232966, either alone or in view of McOmie or the '369 patent.

B. Applicants also respectfully submit that EP 232966, alone or in view of the '393 patent, does not render obvious the claimed aldol condensation.

Applicants' amended claims recite, *inter alia*, the aldol condensation of an aldehyde 17 with a 6-bromo-penem structure 16 in the presence of a Lewis acid and an organic tertiary base. Importantly, Applicants' claims require that the aldol condensation be performed using the 6-bromo-penem structure 16, a compound containing a  $\beta$ -lactam ring as well as the p-nitrobenzyl protecting group. In contrast, the disclosure of EP 232966 is limited to aldol condensation of compounds containing a  $\beta$ -lactam ring using the particular lithium amide bases identified at EP 232966 p. 24, lines 15-17. Moreover, the disclosure of the '393 patent is limited to the aldol condensation of particular chromene compounds having an aliphatic ketone, *i.e.*, wherein the ketone is not found in such a constrained ring.

As such, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness. (MPEP 706.02(j)) First, the Examiner has provided no suggestion or motivation to combine the aldol condensation conditions of the  $\beta$ -lactam-containing compounds of EP 232966 with the aldol condensation conditions of the '393 patent. The aldol condensation conditions of the '393 patent are limited to an aliphatic ketone, and there is no suggestion in either the '393 patent or EP 232966 that the aldol condensation conditions applicable to an aliphatic ketone would be applicable to an aldol condensation of a ketone that is within a constrained ring. Nor is there any suggestion or motivation that the aldol condensation conditions applicable to an aliphatic ketone would be applicable to the constrained  $\beta$ -lactam ring in particular. Second, the Examiner has not provided any reasonable expectation of success. In fact, given the structural dissimilarities between the  $\beta$ -lactam ring of EP 232966 on the one hand, and the aliphatic ketone of the '393 patent on the other hand, one of skill in the art would not have had a reasonable expectation of success, even assuming *arguendo* that EP 232966 and/or the '393 patent provided the requisite suggestion or motivation to combine.

Thus, Applicants' claimed aldol condensation and pending claims related thereto are non-obvious in view of EP 232966, either alone or in view of the '393 patent.

Regarding claims 32-33 and 36-40, Applicants respectfully submit that amended claim 32, which now recites "dissolving 6-aminopenicillanic acid in an organic solvent and water in the presence of hydrobromic acid and sodium or potassium nitrite solution," renders moot the Examiner's rejection.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. § 103.

#### **Double Patenting**

Claims 1-30 and 32-42 stand provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-31, 33-40 of copending U.S. Patent Application No. 10/427,666 ("the '666 Application").

Applicants stand prepared to cancel the relevant claims of the '666 Application when instant claims 1-30 and 32-42 are found to be allowable.

#### **Specification**

The Examiner has objected to the abstract for stating that there is a process, but not stating what the process actually consists of.

Applicants have amended the abstract (*i.e.*, specification p. 239) to recite that the process comprises condensing an aldehyde 17 with 6-bromo-penem derivative of structure 16.

Accordingly, Applicants respectfully request that the Examiner withdraw this objection.

#### **Information Disclosure Statement**

Applicants wish to thank the Examiner for discussing the Information Disclosure Statement filed on October 24, 2003 ("IDS") with Applicants' undersigned representative on February 28, 2006. It is Applicants' understanding that the IDS was not processed in the present application.

Applicants respectfully request that the Examiner consider the references cited in the IDS, make them of record by initialing the PTO Form 1449, and forward a copy with the next communication.

**Conclusion**

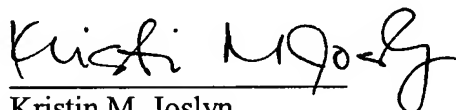
Applicants respectfully submit that the present amendment places the application in condition for allowance. Applicants respectfully request that the Examiner enter the present amendment, and allow the pending claims to issue.

The Director is hereby authorized to charge any fees due in connection with this reply, or credit any overpayment of the same, to Wilmer Cutler Pickering Hale and Dorr LLP Deposit Account No. 08-0219.

Respectfully submitted,

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